INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

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IB/03/4436

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1023/Del/2002*** *dated* ***8th October 2002.***

Witness my hand this 22nd day of December2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1023-2

- 8 OCT 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A METHOD FOR THE PREPARATION OF STABLE GABAPENTIN TABLETS "**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. RAMALINGAM MANIKANDAN

b. ASHISH GOGIA

c. SUNILENDU BHUSHAN ROY

d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, RAMALINGAM MANIKANDAN, ASHISH GOGIA, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India; all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(RAMALINGAM MANIKANDAN)

b.

(ASHISH GOGIA)

c.

(SUNILENDU BHUSHAN ROY)

d.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **684468** dated **13.09.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 8TH day of **OCTOBER,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

1023-2

- 8 OCT 2002

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A METHOD FOR THE PREPARATION OF STABLE GABAPENTIN TABLETS

RANBAXY LABORATORIES LIMITED

19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention is generally directed to a method for the preparation of stable gabapentin tablets.

Gabapentin is an anti-epileptic drug indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin exists in a crystalline form and exhibits poor compressibility and compactibility. These detrimental characteristics of gabapentin cause capping and lamination defects during compression of gabapentin into tablets.

Conventionally these problems can be overcome by incorporating compression aids in the formulation. However, the more excipients used in a composition the more expensive and time-consuming commercial production becomes. Moreover, increasing the amount of excipient results in large sized tablets, which is undesirable in pedriatic use and or in the medication of patients, which have difficulty in swallowing.

The inclusion of large amounts and/or number of excipients to a gabapentin formulation result in stability problems such as degradation. Gabapentin has been found to degrade into lactam, resulting in a decrease in the potency of gabapentin over time. Therefore, it is necessary to avoid degradation of gabapentin over the shelf life of the product. The shelf life of the product is generally two years from completion of manufacture. The level of degradation over the shelf life of the tablets can be determined by storing the product in closed containers for a three-month period at 40°C and 75% relative humidity. Tablets containing gabapentin should have no more than about 0.4% by weight of lactam as determined by High Performance Liquid Chromatography (HPLC) at the end this three-month period.

To combat the lactam formation and provide product stability, US PAT. NO. 6,054,482 discloses the importance of

(a) starting with gabapentin raw material that contains 0.5% or less of corresponding lactam,

(b) not allowing the anion of a mineral acid in the composition to exceed 20 ppm, and

(c) using a specifically selected adjuvant that is not adverse to gabapentin stability.

To achieve all this it discloses a method which entails hydrolyzing gabapentin with a semi concentrated mineral acid and then converting gabapentin into solid pharmaceutical compositions containing hydroxypropylmethylcellulose, polyvinylpyrrolidone; crospovidone, maize starch, cyclodextrin, talcum, co-polymer of dimethylaminomethacrylic acid and/or neutral methacrylic acid ester.

Another difficulty encountered in producing gabapentin tablets is that gabapentin is not amenable to traditional wet granulation techniques. Because the viscosity of the binder solution increases with an increase in the binder content, to apply a functional amount of binder for gabapentin, the amount of solvent has to be increased. This results in a wet granulation that is in a semi-liquid state and is not suitable for conventional drying methods. Therefore, the wet granulation technique has to be done in multiple stages where a portion of binder solution is added, followed by drying, then the next portion of binder solution and so forth.

Purepac in the U. S. Pat. No. 6,294,198 has eliminated this problem by using a spray-coating method wherein a binder is dissolved in a solvent to form a binder solution that

is then spray-coated on the drug particles. By using this method substantially all of the solvent is evaporated as it is applied, leaving a film of binder around the drug particles, and the process is conducted at or below room temperature.

We have now discovered that the stable gabapentin tablets can be prepared easily by a wet granulation method and that too without having to use the gabapentin having anion of a mineral acid (calculated as chloride content) less than 20 ppm.

The resulting tablets are not only free from capping and lamination defects but also have better hardness and are stable.

Therefore, the present invention relates to a wet granulation method for preparing stable gabapentin tablet wherein the wet granulation comprises:
(i) dry mixing a part of binder as defined herein with gabapentin or other conventional excipient(s) or both;
(ii) granulating the above mixture with remaining part of the binder dissolved/suspended in a suitable solvent as defined herein.

The wet granulation method of the present invention is unique as it involves dry mixing of a part of binder with drug or other excipients or both; and adding rest of the binder in the form of solution/dispersion.

The addition of binder in two portions is advantageous. Firstly, the quantity of solvent used for preparing binder solution is reduced to the minimum, which makes it possible to add binder solution in a single step. It also reduces duration of exposure of gabapentin to the solvent, which further helps to reduce chances of polymorph conversion and or changes in crystal structure in gabapentin. Secondly, since the use of solvent is minimum, it is safe and environment friendly.

The wet granulation method of the present invention may be applied to other active drugs as well, which have poor compressibility and compactibility.

In the present invention any binder, which is compatible with gabapentin may be used. For examples binder may be selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, Copolyvidone, sugars or a combination thereof. The binder may be dissolved/ dispersed in solvent such as water alone or mixture of water with ethanol or isopropyl alcohol or acetone. The concentration of binder in solution will depend upon the components used and the desired viscosity. Normally the Drug: Binder ratio may vary from about 1:0.01 to about 1:1.

The binder solution/dispersion may be prepared by any method that permits dissolution of binder to produce a homogenous solution, mixture or dispersion, such that formulations may be prepared that will contain a uniform amount of the binder.

For the purpose of the present invention Gabapentin may be present as a free base, hydrated form such as monohydrate or any other pharmaceutically acceptable salt thereof. Anion of the mineral acid (calculated as chloride content) may be up to 100 ppm.

The other excipients may be selected from the group comprising of disintegrant, filler, stabilizer, lubricant, colorants, flavors and glidants.

The disintegrant as used in the present method of the invention may be, but not limited to, microcrystalline cellulose, sodium starch glycolate, crosslinked carboxy

methylcellulose, crospovidone or a combination thereof. The disintegrant may be present intragranularly, as well as extragranularly. The disintegrant may be used in the concentration of about 0.5% w/w to about 15% w/w of the tablet.

The fillers in the invention may be selected from any conventional fillers such as lactose, microcrystalline cellulose, mannitol, dicalcium phosphate or a combination thereof.

The stabilizer in the present invention may be selected from the poloxamer, cremophor or other anionic, cationic, nonionic surfactants or a combination thereof. The stabilizer may be used in concentration of about 0.1% w/w to about 10% w/w of tablet.

The lubricant of the present invention may be selected from the group comprising of magnesium stearate, stearic acid or sodium stearyl fumarate.

The method of the present invention may be carried out using the following steps:

(i) Gabapentin is mixed with disintegrant(s) in a mixer.

(ii) The binder is divided into two portions, one portion is mixed with gabapentin-disintegrant mixture and remaining portion is dissolved in sufficient quantity of granulating solvent to prepare the binder solution.

(iii) The binder solution is then mixed with gabapentin-disintegrant-binder mixture of step (i) in a low shear mixer.

(iv) The granules of step (iii) are dried in a fluidized bed dryer.

(v) The dried granules are mixed with rest of the excipients such as stabilizer, filler, glidants, disintegrant (extragranular) and lubricant and compressed using appropriate tooling.

For ease of swallowing and to enhance the aesthetic appeal, it may be desirable to coat the tablet. It may optionally be coated with hydrophilic polymers such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone and polyvinyl alcohol.

The tablets prepared by the method of the present invention have hardness of about 10 Kp to about 30 Kp and friability of less than 1% w/w.

The lactam content of the gabapentin tablet of present invention after three months of storage at 40°C and 75% relative humidity does not exceed 0.4% by weight of gabapentin.

The following examples are given for purpose of illustrating the present invention and are not intended to limit the scope in any way.

EXAMPLES

CORE

Ingredient	Quantity (mg)	
	Example 1	Example 2
Intragranular		
Gabapentin	800	800
Hydroxypropyl cellulose-L (HPC-L)	40	40
Crospovidone	22	-
Extragranular		
Crospovidone	22	44
Corn starch	60	-
Poloxamer	11	11
Dicalcium phosphate	68	-
Mannitol	110	178
Talc	11	11
Magnesium stearate	16	16

Method:

Example-1: Gabapentin, HPC-L (half quantity) and crospovidone are mixed in a rapid mixed granulator and granulated with HPC-L solution/dispersion in purified water and dried in a fluid bed dryer. The dried granules are mixed with extragranular excipients i.e. crospovidone, corn starch, poloxamer, dicalcium phosphate and mannitol in a low shear blender for 15 minutes. The blend is finally mixed with talc and magnesium stearate in a low shear blender for 10min and compressed with appropriate tooling.

Example-2: Gabapentin and HPC-L (half quantity) are mixed in a rapid mixer granulator and granulated with binder solution (i.e. solution of rest of the quantity of HPC-L in purified water) and dried in a fluid bed dryer. The dried granules are mixed with extragranular excipients i.e. crospovidone, poloxamer and mannitol in a low shear blender for 15 minutes. The blend is finally mixed with talc and magnesium stearate in a low shear blender for 10min and compressed with appropriate tooling.

The tablets made as per the above examples are coated with the given coating composition.

Coating formula:

Hydroxypropylcellulose: 15 mg

Talc: 15mg

Purified water: q.s.

Tablets of Example-2 were subjected to accelerated studies for three months at 40°C and 75% relative humidity (RH); the stability, friability and hardness data is shown in the following Tables:

Stability data of gabapentin tablets subjected to accelerated studies.

	Initial	1M/40°C/75% RH	2M/40°C75% RH	3M/40°C/75 RH
Gabapentin (%w/w)	99.51	97.02	101.4	99.04
Gabapentin lactam derivative (%w/w)	N.D*	0.027	0.139	0.198

*N.D. - Not detected

Friability and Hardness data

Tablet	Friability (% w/w)	Hardness Range (Kp)
Uncoated tablets	0.25	16- 18
Coated Tablets (initial)	0.03	20-24
Coated Tablets (One month at 40°C / 75%RH)	0.00	22-27
Coated Tablets (Two months at 40°C / 75% RH)	0.10	19-24
Coated Tablets (Three months at 40°C / 75% RH)	0.04	20-22

WE CLAIM:

1. A wet granulation method for preparing stable gabapentin tablet wherein the wet granulation comprises:
   (i) dry mixing a part of binder as defined herein with gabapentin or other conventional excipient(s) or both;
   (ii) granulating the above mixture with remaining part of the binder dissolved/suspended in a suitable solvent as defined herein.
2. The method according to claim 1 wherein the binder solution/dispersion is prepared in water alone or mixture of water with ethanol or isopropyl alcohol or acetone.
3. The method according to claim 1 wherein Drug: Binder ratio is 1:0.01 to 1:1 by weight.
4. The method according to claim 2 wherein the binder may be selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, copolyvidone, sugars or a combination thereof.
5. The method according to claim 4 wherein the binder is hydroxypropyl cellulose.
6. The method according to claim 4 wherein the binder is copolyvidone.
7. The method according to claim 1 wherein the other excipients are selected from the group consisting of disintegrant, filler, stabilizer, lubricant, colorants, flavors and glidants.
8. The method according to claim 7 wherein the disintegrant is used in concentration of 0.5% to 15% w/w of the tablet.
9. The method according to claim 8 wherein the disintegrant is crospovidone.
10. The method according to claim 7 wherein he filler may be selected from any conventional fillers such as lactose, microcrystalline cellulose, mannitol, dicalcium phosphate or a combination thereof.
11. The method according to claim 10 wherein the filler is mannitol.
12. The method according to claim 10 wherein the filler is dicalcium phosphate.
13. The method according to claim 10 wherein the stabilizer may be selected from poloxamer, cremophor or other anionic, cationic, nonionic surfactants or a combination thereof.
14. The method according to claim 13 wherein stabilizer is present in concentration of 0.1% w/w to 10% w/w of the tablet.

15. The method according to claim 13 wherein the stabilizer is poloxamer.

16. The method according to claim 7 wherein the lubricants are selected from the group consisting of magnesium stearate, stearic acid and stearyl fumarate.

17. The method according to claim 16 wherein the lubricant is magnesium stearate.

18. A wet granulation method for the preparation of stable gabapentin tablets substantially described and exemplified herein.

Dated this 8TH day of **October, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary